

PAPER

The management of refractory generalised convulsive and complex partial status epilepticus in three European countries: a survey among epileptologists and critical care neurologists

M Holtkamp, F Masuhr, L Harms, K M Einhäupl, H Meierkord, K Buchheim

J Neurol Neurosurg Psychiatry 2003;74:1095–1099

See end of article for authors' affiliations

Correspondence to:
Dr M Holtkamp,
Department of Neurology,
University Hospital Charité,
Schumannstr 20/21,
10117 Berlin, Germany;
martin.holtkamp@charite.de

Received
13 November 2002
In revised form 5 March
2003
Accepted 9 March 2003

Objective: To survey the current clinical treatment of refractory status epilepticus and to identify steps in its management which may need further investigation.

Methods: Epileptologists and critical care neurologists were surveyed using a standardised postal questionnaire.

Results: Sixty three of 91 participants (69%) returned the questionnaires. Two thirds of the respondents applied another non-anaesthetising anticonvulsant after failure of first line drugs. General anaesthesia for ongoing complex partial status epilepticus (CPSE) was part of the therapeutic regimen of 75% of the interviewees. A non-barbiturate as general anaesthetic of first choice was used by 42%. Up to 70% titrated the anaesthetic to achieve a burst suppression pattern in the electroencephalogram, indicating deep sedation, and 94% reduce anaesthesia within 48 hours.

Conclusions: The management of refractory status epilepticus is heterogeneous in many aspects, even among clinicians who are most familiar with this severe condition. Randomised trials are needed to compare the efficacy, side effects, optimal duration, and depth of general anaesthesia.

Status epilepticus, the maximum expression of epilepsy, is an important neurological emergency. Generalised convulsive status epilepticus is the most common and dangerous type, as the condition may have severe systemic consequences including hyperthermia, acidosis, hypoxia, and changes in blood pressure.^{1,2} The neurological sequelae may also be very serious with focal neurological deficits, intellectual deterioration, and chronic epilepsy.³ Indeed, clinical and experimental studies have shown significant functional and structural damage, preferentially in the hippocampus but also in various other brain regions.⁴ The condition is not rare, with estimated incidence rates of between 10 and 41 per 100 000.^{3,5–8} Variable rates of mortality and morbidity for status epilepticus have been reported, depending on the underlying aetiology. Case fatality may be between 7.6% and 19% within the first 30 days.^{5,7,9} In unprovoked status epilepticus, a lower mortality of 4.7% has been reported.⁹ Morbidity may range from 3.4% to 12.5%.^{10,11} In addition, acute symptomatic status epilepticus carries a higher risk for subsequent unprovoked seizures compared with short lasting acute symptomatic seizures.¹²

With these features in mind, there is general agreement that immediate and effective treatment is required. First line anticonvulsants like benzodiazepines and phenytoin fail to terminate status epilepticus in 31–50% of cases.^{13,14} Status epilepticus continuing after such failure becomes refractory, and is thus an even more difficult clinical problem.¹⁴

In spite of the common occurrence and grave prognosis of status epilepticus there is no consensus in published reports over the therapeutic management of cases refractory to first line antiepileptic drugs, and no national or international guidelines have been released. As we were interested in the current management of this condition, we conducted a survey in three German speaking countries.

Although the first line treatment of this condition is mostly undertaken by emergency physicians, neurologists are often involved in the management of refractory cases. We surveyed neurologists who were especially involved in the treatment of refractory status epilepticus—that is, critical care neurologists

and epileptologists. Our aim was to provide an overview of current clinical practice and to identify steps in the management of refractory status epilepticus which need further validation through controlled clinical trials.

METHODS

The survey was undertaken in Austria, Germany, and Switzerland among neurologists specialising in critical care medicine or epileptology. We included all opinion leaders, as defined along the lines suggested by Borbas *et al.*¹⁵ All were members of the particular chapter of the International League Against Epilepsy or of the Society of Critical Care Neurology and in a leading position, being responsible for the treatment of status epilepticus in a neurological department of an acute care hospital or in a specialised epilepsy centre. We decided not to conduct a cross sectional survey interviewing a random sample of all neurologists, as complex conditions such as refractory status epilepticus are primarily treated by specialists.

The survey was conducted through a postal questionnaire between July 2001 and February 2002. Participants who did not respond to the first mailing were addressed a second time.

We defined status epilepticus as refractory if a patient was unresponsive to first line treatment with benzodiazepines and (fos-)phenytoin or valproic acid, independently of the time elapsed since the onset of status epilepticus. The participants were asked to indicate the next steps in the patient management usually taken under their care. Figure 1 outlines the main questions schematically, and fig 2 shows the translated questionnaire.

The questionnaire contained two questions characterising the interviewee and the monitoring facilities of the institution, and five main questions concerning the further management of status epilepticus after the failure of first line agents: the next therapeutic step; the point when the decision is made that general anaesthesia should be induced; the preferred anaesthetics used; the titration goal when using anaesthetics; and the point at which reduction of anaesthetisation begins.

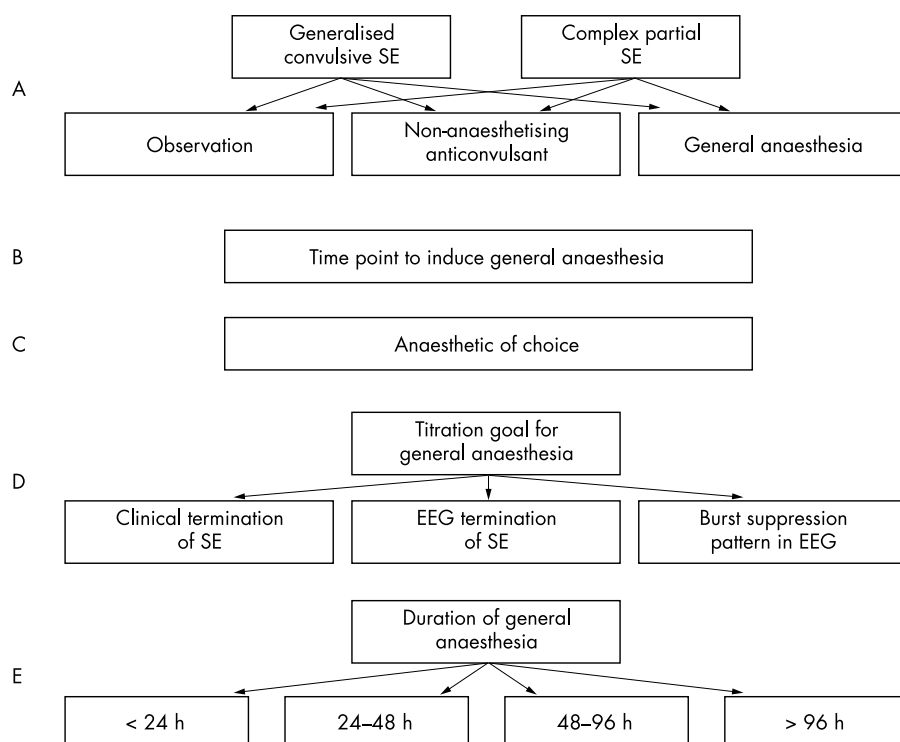


Figure 1 Schematic outline of the questionnaire employed. What are the next steps following failure of first line anticonvulsants in the treatment of generalised convulsive and complex partial status epilepticus: further observation, application of another non-anaesthetising anticonvulsant, or immediate induction of general anaesthesia? (A). If general anaesthesia is part of the therapeutic regimen, the interviewees were asked at what point after the onset of the condition this is induced in either form of status epilepticus (B), and what is their anaesthetic of choice (C). The next question refers to the titration goal aimed at: clinical termination of status epilepticus, electroencephalographic (EEG) termination, or deep sedation indicated by an EEG burst suppression pattern (D). Finally, we asked how long the maximum dosage of the anaesthetic agent is given before stepwise reduction is initiated (E). SE, status epilepticus.

The frequency distributions were analysed for generalised convulsive and complex partial status epilepticus separately whenever the survey differentiated between these two forms. The given percentages of participants are related to the number of valid answers (n) to each specific question. Differences were tested for significance using analysis of variance or Fisher's PLSD where appropriate.

RESULTS

Overall, 63 of 91 interviewees (69%) responded to the survey. Questionnaires were returned by 37 critical care neurologists and by 26 epileptologists. Two of the epileptologists returned blank questionnaires as their medical centres lacked an intensive care unit and thus could not provide adequate facilities for the treatment of refractory status epilepticus.

The answers given by epileptologists and critical care neurologists were not significantly different, so the data are presented together.

Procedure after failure of first line anticonvulsants

In considering the failure of first line drugs we differentiated between generalised convulsive and complex partial status epilepticus. We offered three options: (1) further observation, (2) application of another non-anaesthetising anticonvulsant, or (3) immediate induction of general anaesthesia. For generalised convulsive status epilepticus, none of the respondents would follow option (1), whereas 20% of the responding physicians would do so in complex partial status epilepticus ($p < 0.001$). Most respondents would apply another non-anaesthetising anticonvulsant for both generalised convulsive (65%) and complex partial status epilepticus (64%). A general anaesthetic was significantly more often used in generalised convulsive than in complex partial status epilepticus (35% v 16%; $p = 0.02$) if first line anticonvulsants failed to terminate the seizures (fig 3A). The non-anaesthetising drug of choice was phenobarbitone

(phenobarbital) in concentrations ranging from 600 to 1200 mg (72% in generalised convulsive status epilepticus and 56% in complex partial status epilepticus). Single respondents would use lignocaine (lidocaine), chloral hydrate, clomethiazol, and magnesium, respectively. Interestingly, in complex partial status epilepticus 22% of the participants give an oral anticonvulsant after failure of intravenous first line drugs.

Time point of induction of general anaesthesia after failure of first line drugs, and preferred anaesthetic

Induction of general anaesthesia during ongoing seizure activity was part of the therapeutic regimen of all questioned participants in patients with generalised convulsive status epilepticus and was used by 75% in cases of complex partial status epilepticus. In generalised convulsive status epilepticus, half the respondents proceeded to general anaesthesia within 30 minutes of the onset of the condition. Most of the participants (61%) withhold general anaesthesia in cases of complex partial status epilepticus until more than one hour has elapsed after seizure onset, whereas only 21% would wait as long as this in patients with generalised seizures ($p < 0.0001$). The data are summarised in fig 3B. Many of the participants answered that they chose general anaesthesia independently of the time course if patients show signs of aspiration or respiratory failure.

The preferred first choice agents were barbiturates (58%), predominantly thiopentone (thiopental), but propofol was a first line drug for 29% of all interviewees, and one of seven respondents gave intravenous midazolam as the first anaesthetising drug (fig 3C). Almost two thirds (58%) recommended propofol as the second choice agent. Ketamine and isoflurane were chosen by only a few respondents.

For this particular question the survey did not differentiate between generalised convulsive and complex partial status epilepticus.

Refractory status epilepticus

(Multiple choices are possible; if you cannot answer a question, please leave the field blank)

1. You are involved in the treatment of refractory status epilepticus:

- () as an intensive care neurologist
() as an epileptologist

2. Given a patient with continuing (a) generalised convulsive or (b) complex partial status epilepticus, although adequate dosages of intravenous benzodiazepines, phenytoin or fosphenytoin and/or valproic acid had been administered and pseudostatus epilepticus was excluded. What would you do next?

| status epilepticus: | (a) generalised convulsive | | (b) complex partial | |
|---------------------------------------|----------------------------|------|---------------------|------|
| I) further observation | | | | |
| II) non anaesthetising anticonvulsant | substance | dose | substance | dose |
| 1. choice | | | | |
| 2. choice | | | | |
| 3. choice | | | | |
| III) general anaesthesia | | | | |

3. The status epilepticus still continues. After what time interval or in which situation would you go for general anaesthesia, if not already performed (see 2 II)?

| status epilepticus: | (a) generalised convulsive | (b) complex partial |
|--|----------------------------|---------------------|
| never | | |
| < 30 min | | |
| 30 – 60 min | | |
| > 60 min | | |
| In which situation independent from duration | | |

4. What is your preferred anaesthetic for the treatment of refractory status epilepticus (generalised convulsive or complex partial)?

| | substance | dose (bolus, infusion) |
|-----------|-----------|------------------------|
| 1. choice | | |
| 2. choice | | |
| 3. choice | | |

5. Which facilities of EEG-monitoring are available in your department?

- () intermittent
() continuous

6. The maximum dose of the general anaesthetic (depth of anaesthesia) is adjusted to:

- () clinical seizure termination
() EEG seizure termination
() occurrence of burst-suppression pattern

7. Reduction of the maximum dosage of the general anaesthetic is started:

- () within the first 24 h
() between 24 and 48 h
() between 48 and 96 h
() at the earliest after 96 h

8. Your comments

Name: _____

Institution: _____

Thank you very much for your participation. Please, send the questionnaire back until the 31.08.2001 in the prepaid envelope.

Dr. Martin Holtkamp
Neurologische Klinik und Poliklinik
Universitätsklinik Charité Berlin
Schumannstraße 20/21
10117 Berlin

Figure 2 The translated questionnaire

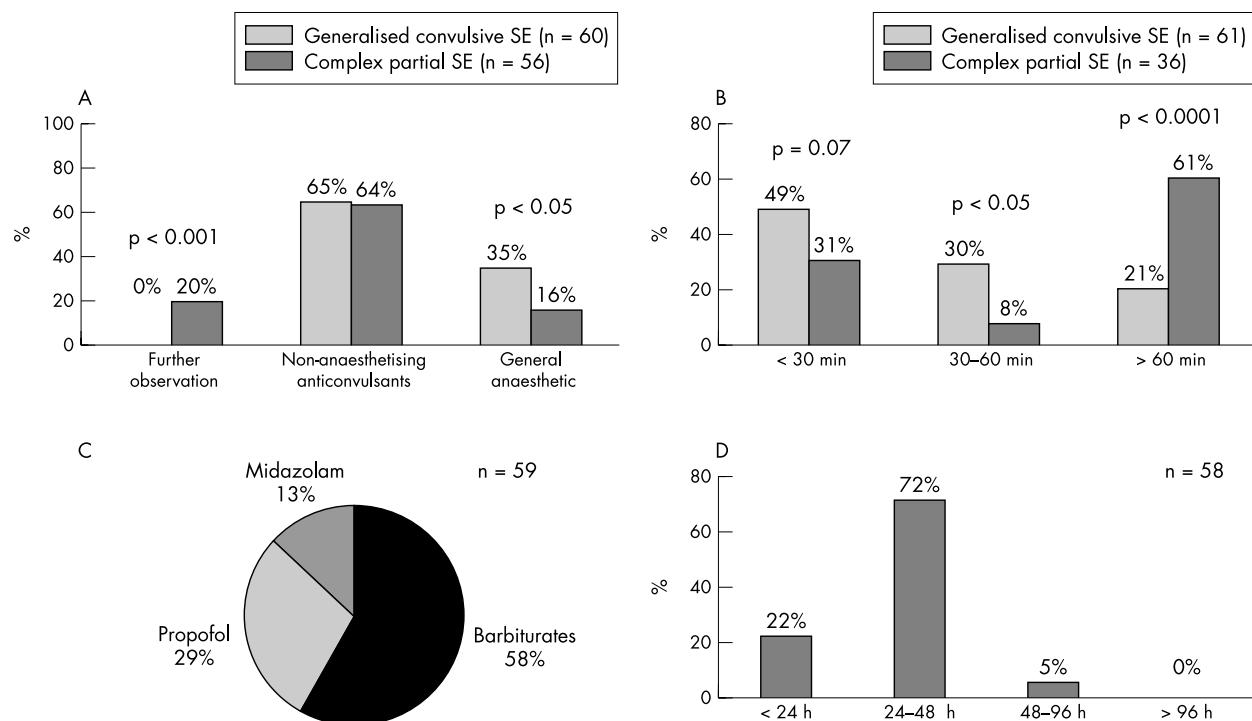


Figure 3 Illustration of four of the main results. (A) Next steps after failure of first line anticonvulsants in generalised convulsive and complex partial status epilepticus (SE). (B) Time point after onset of status epilepticus at which general anaesthesia is induced. (C) Frequency distribution of the anaesthetic of choice in refractory status epilepticus, as indicated by the participants. (D) Distribution of time frames at which general anaesthesia is reduced. Note that not a single expert sustained a maximum dose of the anaesthetic for more than 96 hours.

Titration goal for general anaesthetics and time point of reduction

Continuous electroencephalographic (EEG) monitoring facilities were available for the vast majority of participants (83%). The survey asked whether the titration goal of general anaesthetics was either clinical or electrophysiological seizure termination, or a burst suppression pattern in the EEG. Multiple answers were allowed. Though continuous EEG monitoring was available for the vast majority, 34% of participants strove only for clinical seizure termination in some patients; 63% sometimes aimed for electrophysiological seizure termination; and 69% increased the dose of the general anaesthetic agent to induce a burst suppression pattern in the EEG.

Epileptic activity may re-emerge after successful clinical and electrophysiological termination of status epilepticus during the phase in which anaesthesia is reduced. Therefore the participants were asked about the duration of general anaesthesia before reduction is initiated. The vast majority of respondents (72%) reported that they reduced the drug dose within 24 to 48 hours, whereas 22% did so during the first 24 hours. Only 5% of all respondents reported a reduction of general anaesthesia within 48 to 96 hours and none would wait for more than 96 hours (fig 3D).

DISCUSSION

The management of refractory status epilepticus lacks clear guidelines and therapeutic approaches are mainly based on the individual experiences of treating physicians. A previous survey among anaesthetists and intensive care physicians in the United Kingdom revealed insufficient therapeutic and monitoring strategies for refractory status epilepticus.¹⁶ We surveyed critical care neurologists and epileptologists because we expected them to be more familiar with this extreme form of epilepsy. The most interesting results of our survey are, first, that three quarters of the responders recommended general anaesthesia for refractory complex partial status epilepticus; second, that more than 40% give non-barbiturate agents; and

third, that two thirds choose burst suppression pattern as an electroencephalographic titration goal, and the vast majority reduce anaesthesia within 48 hours.

All participants reported that they treated patients with generalised convulsive status epilepticus more vigorously than complex partial status, proceeding rapidly to general anaesthesia in the former. This result is not unexpected given the potentially severe systemic and neurological consequences of generalised convulsive status epilepticus. However, a large number of participants (75%) recommended general anaesthesia for ongoing complex partial status epilepticus as part of their therapeutic regimen. This was surprising because aggressive management of this condition remains controversial and there is dispute over the degree of transient or permanent deficit left in its wake. Valid animal models have shown cell loss in both hippocampal and extrahippocampal regions,¹⁷ and severe and permanent neurological deficits have been reported in humans.^{18–19} However, a poor outcome of complex partial status epilepticus has been attributed to comorbidity, and possibly overtreatment,²⁰ as general anaesthesia is associated with a high mortality²¹ and carries significant risks of hypotension, hypothermia, and immunosuppression.^{22–23} Therefore, some clinicians claim that the risk of persistent neurological deficits after complex partial status epilepticus must be balanced against the risks of general anaesthesia.^{20–24}

Most respondents preferred barbiturates for general anaesthesia in refractory status epilepticus. The results of a recent systematic review suggest a higher efficacy of pentobarbitone compared with midazolam and propofol combined.²⁵ However, pentobarbitone treatment was more often titrated to EEG background suppression than treatment with other agents, and the titration goal may have an impact on the effectiveness of a chosen treatment regimen.

Propofol was the anaesthetic of first choice for almost one third of the participants, although it may have pro-convulsive properties and its use for general anaesthesia in patients with epilepsy is controversial.²⁶ Within recent years, however, an increasing number of case reports and one small uncontrolled

series have described benefit from propofol anaesthesia in patients with refractory status epilepticus.²⁷ There are also experimental data demonstrating the strong anticonvulsive properties of propofol.²⁸ It appears capable of controlling refractory status epilepticus in responsive patients more quickly than high dose barbiturates.²⁷

One of seven participants chose midazolam as a general anaesthetic for refractory status epilepticus. A retrospective study showed that refractory non-convulsive status epilepticus is terminated in 82% of cases within 60 minutes after intravenous application. However, breakthrough seizures, usually detectable only by continuous EEG monitoring, occurred in over half the patients after more than six hours of midazolam treatment.²⁹ Thus a high relapse rate seems to be the major limitation of midazolam use in refractory status epilepticus.

Most respondents give the anaesthetic in high dosage, aiming at a burst suppression pattern which is maintained for less than 48 hours. The depth and duration of anaesthesia have been addressed in two retrospective studies only. Higher dosages of the anaesthetic were associated with less likelihood of recurrence of seizure activity and a better clinical outcome overall.³⁰ Maintenance of general anaesthesia for more than 96 hours resulted in a lower relapse rate and a significantly better survival compared with shorter durations.³¹ However, it remains an open question whether prolonged and deep general anaesthesia is justified, considering the severe side effects. There is no prospective study assessing relative efficacy and morbidity when electrographic seizure termination, burst suppression pattern, and electrocerebral silence are compared as EEG end points.

Conclusions

This survey showed that the management of refractory status epilepticus is quite variable, even among physicians who are most familiar with this severe condition. It is reasonable to assume that a population based survey among critical care physicians, neurologists, and epileptologists would have even more heterogeneous results. To improve the management of refractory status epilepticus, randomised trials comparing the efficacy and side effects of treatment agents and assessing the optimal duration and depth of general anaesthesia are needed.

APPENDIX

List of participants

H Baier, *Ulm*; C Baumgartner, *Vienna*; J Berrouschot, *Leipzig*; R Besser, *Krefeld*; F Block, *Aachen*; U Bogdahn, *Regensburg*; U Bompitz, *Schwerin*; P Bülow, *Waldbreitbach*; W Christe, *Potsdam*; J Claßen, *Rostock*; G Dittmar, *Dortmund*; F Dömgies, *Mönchengladbach*; E Dülz, *Magdeburg*; F Erbguth, *Nürnberg*; J H Faiss, *Teupitz*; B Findeis, *Lobetal*; H Frost, *Cologne*; J v Giesen, *Düsseldorf*; J Glahn, *Minden*; H C Hansen, *Neumünster*; H P Harig, *Linz*; W Haupt, *Cologne*; A Hufnagel, *Essen*; R W C Janzen, *Frankfurt/M*; J M Klotz, *Fulda*; W Koch, *Bremen*; K Krakow, *Frankfurt/M*; G Krämer, *Zürich*; H K Kursawe, *Potsdam*; C Lassek, *Kassel*; H-J Meencke, *Berlin*; W Müllges, *Würzburg*; M Neumann, *Erfurt*; M Nüchel, *Giessen*; B Pohlmann-Eden, *Mannheim*; H Prange, *Göttingen*; F Reinhardt, *Erlangen*; W Rimpau, *Berlin*; T Rösel, *Karlsruhe*; F Rosenow, *Marburg*; J Röther, *Hamburg*; U Runge, *Greifswald*; C Schiel, *Giessen*; J Schäfer, *Bonn*; K Schleglmann, *Augsburg*; E Schmutzhard, *Innsbruck*; R Schreiner, *Munich*; A Schulze-Bonhage, *Freiburg*; S Schwab, *Heidelberg*; G Seidel, *Lübeck*; R Seitz, *Düsseldorf*; H Stefan, *Erlangen*; B Steinhoff, *Kehl-Kork*; M Stephan, *Halle*; R Stingle, *Kiel*; F Tergau, *Göttingen*; B Tettenborn, *St Gallen*; S Varosanec, *Bruck*; P Velho-Groneberg, *Munich*; A Wiborg, *Günzburg*; H G Wieser, *Zürich*; O W Witte, *Jena*; P Wolf, *Bielefeld*

Authors' affiliations

M Holikamp, F Masuhr, L Harms, K M Einhäupl, H Meierkord, K Buchheim, Department of Neurology, University Hospital Charité, Humboldt University, Berlin, Germany

Martin Holikamp and Florian Masuhr contributed equally to this work.

Competing interests: none declared

REFERENCES

- Wasterlain CG, Fujikawa DG, Penix L, *et al*. Pathophysiological mechanisms of brain damage from status epilepticus. *Epilepsia* 1993;**34**(suppl 1):S37–53.
- Meldrum BS, Horton RW. Physiology of status epilepticus in primates. *Arch Neurol* 1973;**28**:1–9.
- Shorvon S. Tonic clonic status epilepticus. *J Neurol Neurosurg Psychiatry* 1993;**56**:125–34.
- Meldrum BS, Brierley JB. Prolonged epileptic seizures in primates. Ischemic cell change and its relation to ictal physiological events. *Arch Neurol* 1973;**28**:10–17.
- Knake S, Rosenow F, Vescovi M, *et al*. Incidence of status epilepticus in adults in Germany: a prospective, population-based study. *Epilepsia* 2001;**42**:714–18.
- DeLorenzo RJ, Hauser WA, Towne AR, *et al*. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. *Neurology* 1996;**46**:1029–35.
- Coeytaux A, Jallon P, Galabardes B, *et al*. Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR). *Neurology* 2000;**55**:693–7.
- Hesdorffer DC, Logroscino G, Cascino G, *et al*. Incidence of status epilepticus in Rochester, Minnesota, 1965–1984. *Neurology* 1988;**50**:735–41.
- Logroscino G, Hesdorffer DC, Cascino G, *et al*. Short-term mortality after a first episode of status epilepticus. *Epilepsia* 1997;**38**:1344–9.
- Cascino GD, Hesdorffer D, Logroscino G, *et al*. Morbidity of nonfebrile status epilepticus in Rochester, Minnesota, 1965–1984. *Epilepsia* 1998;**39**:829–32.
- Aminoff MJ, Simon RP. Status epilepticus. Causes, clinical features and consequences in 98 patients. *Am J Med* 1980;**69**:657–66.
- Hesdorffer DC, Logroscino G, Cascino G, *et al*. Risk of unprovoked seizure after acute symptomatic seizure: effect of status epilepticus. *Ann Neurol* 1998;**44**:908–12.
- Treiman DM, Meyers PD, Walton NY, *et al*. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med* 1998;**339**:792–8.
- Mayer SA, Claassen J, Lokin J, *et al*. Refractory status epilepticus: frequency, risk factors, and impact on outcome. *Arch Neurol* 2002;**59**:205–10.
- Borbas C, Morris N, McLaughlin B, *et al*. The role of clinical opinion leaders in guideline implementation and quality improvement. *Chest* 2000;**118**:24–325.
- Walker MC, Smith SJ, Shorvon SD. The intensive care treatment of convulsive status epilepticus in the UK. Results of a national survey and recommendations. *Anaesthesia* 1995;**50**:130–5.
- Hosford DA. Animal models of nonconvulsive status epilepticus. *J Clin Neurophysiol* 1999;**16**:306–13.
- Engel J, Ludwig BI, Fetell M. Prolonged partial complex status epilepticus: EEG and behavioral observations. *Neurology* 1978;**28**:863–9.
- Krumholz A, Sung GY, Fisher RS, *et al*. Complex partial status epilepticus accompanied by serious morbidity and mortality. *Neurology* 1995;**45**:1499–504.
- Kaplan PW. Assessing the outcomes in patients with nonconvulsive status epilepticus: nonconvulsive status epilepticus is underdiagnosed, potentially overtreated, and confounded by comorbidity. *J Clin Neurophysiol* 1999;**16**:341–52.
- Lowenstein DH, Aminoff MJ, Simon RP. Barbiturate anesthesia in the treatment of status epilepticus: clinical experience with 14 patients. *Neurology* 1988;**38**:395–400.
- Chesnut RM, Marshall LF. Management of severe head injury. In: Ropper AH, ed. *Neurological and neurosurgical intensive care*. New York: Raven Press 1993:203–46.
- Rashkin MC, Youngs C, Penovich P. Pentobarbital treatment of refractory status epilepticus. *Neurology* 1987;**37**:500–3.
- Aminoff MJ. Do nonconvulsive seizures damage the brain? – No. *Arch Neurol* 1998;**55**:119–20.
- Claassen J, Hirsch LJ, Emerson RG, *et al*. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia* 2002;**43**:146–53.
- Sneyd JR. Propofol and epilepsy. *Br J Anaesth* 1999;**82**:168–9.
- Stecker MM, Kramer TH, Raps EC, *et al*. Treatment of refractory status epilepticus with propofol: clinical and pharmacokinetic findings. *Epilepsia* 1998;**39**:18–26.
- Holikamp M, Tong X, Walker MC. Propofol in subanesthetic doses terminates status epilepticus in a rodent model. *Ann Neurol* 2001;**49**:260–3.
- Claassen J, Hirsch LJ, Emerson RG, *et al*. Continuous EEG monitoring and midazolam infusion for refractory nonconvulsive status epilepticus. *Neurology* 2001;**57**:1036–42.
- Krishnamurthy KB, Drislane FW. Depth of EEG suppression and outcome in barbiturate anesthetic treatment for refractory status epilepticus. *Epilepsia* 1999;**40**:759–62.
- Krishnamurthy KB, Drislane FW. Relapse and survival after barbiturate anesthetic treatment of refractory status epilepticus. *Epilepsia* 1996;**37**:863–7.